

EDITORIAL REVIEWS

Plaque Disruption and the Acute Coronary Syndromes of Unstable Angina and Myocardial Infarction: If the Substrate Is Similar, Why Is The Clinical Presentation Different?*

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In a majority of instances, both unstable angina and acute myocardial infarction occur secondary to plaque disruption and thrombus formation. Although the pathogenetic substrates are similar the clinical presentations are quite different. It is hypothesized in this editorial review that the amount of acute thrombus formation and specifically fibrin deposition is greater in myocardial infarction than in unstable angina. Both angiographic studies and studies analyzing the response to thrombolytic agents suggest more thrombus in myocardial infarction than in unstable angina.

These data have recently been substantiated by angiographic observations in these acute syndromes suggesting that more platelet-rich (whitish) thrombus occurs in unstable angina and more red thrombus in myocardial infarction. The red thrombus presumably would be more responsive to thrombolytic agents.

Furthermore, it is proposed that these differences between syndromes in acute thrombus formation can be explained by the interplay of vessel wall injury, coagulation variables or stasis of blood flow occurring at or after the time of presentation.

Therefore, acute myocardial infarction is associated with occlusive, fibrin-rich thrombus, whereas in unstable angina, the thrombus is nonocclusive, mural and possibly more platelet-rich. However, the clinical syndrome that ultimately develops after plaque disruption is dependent not only on the amount of acute thrombus formation but on the net result of all factors that influence the balance between coronary blood supply and myocardial oxygen demand.

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Although plaque disruption with thrombus formation has been suggested as the major pathogenetic mechanism for the acute coronary syndromes of unstable angina and myocardial infarction, the determinants of which syndrome a patient will develop after disruption are incompletely understood. Furthermore, because it has been postulated (1) that most plaque fissures are asymptomatic and result only in slow progression of atherosclerotic lesions, it is also unclear what determines whether plaque disruption leads to an acute clinical syndrome. We (2,3) and others (4) have suggested that the syndrome ultimately developed by a patient after plaque disruption depends on many factors such as the degree and acuteness of obstruction, the duration of decreased perfusion and the relative myocardial oxygen demand as well as the collateral circulation. Whether or not there are different pathophysiologic determinants explaining these differences among syndromes is also unknown. In this editorial the amount and perhaps even the composition of

intracoronary thrombus is suggested as a major pathophysiologic difference between unstable angina and acute myocardial infarction. It is hypothesized that in myocardial infarction the thrombus is larger and more fibrin rich than the thrombus seen in unstable angina.

Thrombus Formation in Myocardial Infarction and Unstable Angina

Acute Myocardial Infarction

There is little doubt that thrombus is the major cause of myocardial infarction. Although most of the pathologic data relating thrombus to myocardial infarction have been obtained from patients presenting with transmural infarction (not to be confused with Q wave infarction) (5,6), angiographic (7,8), biochemical (9,10), pharmacologic (11,12) and surgical (7) data indicate that thrombus is the major cause of both Q wave and non Q wave myocardial infarction. When thrombus is found in the coronary arteries, pathologic studies (13) usually indicate a disrupted atherosclerotic plaque in 75% of cases and the presence of superficial intimal injury in the remaining 25%. Thrombus at the site of disruption is platelet rich. Thrombus extending distal and even proximal to the site of disruption at a site of total occlusion is fibrin and red cell rich. Falk (14) showed that coronary thrombus in patients with unstable angina and a fatal outcome has a

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layered structure with thrombotic material of different ages indicating episodic growth. Total occlusion of the infarct-related artery on angiography is found in up to 90% of patients presenting within the 1st 6 h of acute myocardial infarction with ST segment elevation on electrocardiogram (7). Recanalization by pharmacologic, mechanical or surgical techniques in these patients indicates acute thrombus formation superimposed on a preexisting stenosis.

Angiographic data also support the importance of thrombus formation in patients presenting with non-Q wave infarction. In the Thrombolysis in Myocardial Infarction trial (TIMI 3A) (unpublished oral presentation 40th Annual Scientific Session, American College of Cardiology, Atlanta, Georgia, March 1991), thrombolytic therapy was administered to patients presenting with either non-Q wave infarction or unstable angina. In most cases a clinical diagnosis of non-Q wave infarction was associated with angiographic evidence of thrombus formation. In addition, the presence of non-Q wave infarction was associated with angiographic improvement after intravenous administration of recombinant tissue-type plasminogen activator (rt-PA). These data are consistent with prior angiographic information (15) indicating the presence of either total occlusion or complex plaque and thrombus in nearly all culprit arteries after recent non-Q wave infarction.

Unstable Angina

The importance of thrombus formation in unstable angina has been underscored by several publications citing angiographic (16-19), angiographic (20-22) and biochemical (10,23,24) data. There are few pathologic studies in patients who died after unstable angina. In a selected group of patients with unstable angina who died and were found on pathologic sectioning to have acute coronary thrombosis, 80% manifested plaque disruption with layered thrombus (14). More recently, Kragel et al. (25) studied 14 patients who died after unstable angina and found a high incidence of total coronary occlusion with multiluminal channels as the most common pathologic finding. However, sectioning of the coronary arteries was performed at 5-mm intervals as opposed to 0.2 or 0.3 mm in the study by Falk (14), and a small area of plaque disruption could conceivably have been missed in some patients.

Angiographic studies in unstable angina detect thrombus in up to 85% of cases (whether thrombus is defined as the presence of a complex lesion or by an intraluminal filling defect). The diagnosis of unstable angina includes patients with different clinical syndromes. If one defines unstable angina as the new onset of low work load or rest angina or an abrupt change in angina that had previously been stable, the incidence of complex plaque and thrombus in the culprit vessel is approximately 70% on angiographic analysis. In patients with a short duration of unstable angina or with very recent onset of rest pain, the incidence of thrombus has been reported to be even higher (26). When other definitions are

used—for example, rest pain slowly progressing over time from a more stable course—the incidence of complex plaque and thrombus will be less. Moreover, angiography is relatively less sensitive than coronary angiography, which has demonstrated an even higher incidence of mural thrombus in patients presenting with unstable angina (21,22). Thrombus visualization on angiography is rare in patients with stable angina.

Evidence Suggesting More Thrombus in Myocardial Infarction Than in Unstable Angina

I. Angiography

The incidence of angiographic total occlusion of the culprit lesion after the onset of an acute coronary syndrome suggests possible differences in the pathologic coronary substrate. There is a progressive increase in the incidence of angiographic total occlusion from about 10% in patients with unstable angina to 80% to 90% in those with acute myocardial infarction with associated ST segment elevation. In patients with non-Q wave infarction, the incidence of total coronary occlusion ranges between 20% and 40%. There is no reason to believe that the higher incidence of total occlusion within the first few hours of a Q wave infarction compared with the incidence in other acute syndromes reflects a more severe underlying stenosis. Pathologic studies in patients with coronary thrombosis (5), serial angiographic studies in selected patients (27,28) and angiographic studies performed after thrombolytic therapy (29,30) indicate that a mild to moderate stenosis commonly precedes or underlies a large proportion of coronary occlusions in patients presenting with unstable angina or a Q wave or non-Q wave infarction. Furthermore, a prospective angiographic study from the Mayo Clinic (31) showed that severe stenosis often proceeded to total occlusion without the development of myocardial infarction. On the other hand, infarction usually developed from a lesion that was <75% occlusive at the time of the initial angiographic study.

Therefore, the higher incidence of angiographic total occlusion after myocardial infarction than after unstable angina suggests, at least to me, a more acute event within the coronary arteries. Intuitively, because the clinical presentation of myocardial infarction is more profound than that of unstable angina, one might expect a more sudden decrease in coronary perfusion after infarction as might occur with an occlusive thrombus.

II. Response to Thrombolytic Therapy

Angiographic studies performed before and after thrombolytic therapy in patients with acute myocardial infarction indicate a 60% to 75% incidence of reperfusion after 90 min with either intracoronary or intravenous thrombolytic therapy. In unstable angina, thrombolytic therapy has been

shown to have only limited angiographic benefit (32-35). The best results occur in that small proportion of patients with unstable angina who are found to have angiographic total coronary occlusion. In contrast, most studies suggest no more than minimal angiographic improvement when the ischemia-related artery is <100% occluded. In the recent TIMI 3A trial (unpublished oral presentation, 40th Annual Scientific Session, American College of Cardiology, Atlanta, Georgia, March 1991), a diagnosis of non-Q wave infarction but not unstable angina was associated with angiographic improvement after intravenous rt-PA.

III. Angioscopy

Angioscopic imaging in the acute coronary syndromes has only recently been reported. Initial studies (21,22) reported a high incidence of intracoronary thrombus but did not try to differentiate the type of thrombus associated with different syndromes. Mizuno et al. (36), utilizing a percutaneous angioscope passed over an angioplasty guide wire, showed a 93% incidence of intracoronary thrombus in 16 consecutive patients presenting with unstable angina. The incidence of thrombus in myocardial infarction was similar. Of interest, the thrombus seen in unstable angina was pale whitish-gray in 71% of arteries, whereas red or mixed white and red thrombus was seen in all 15 patients with acute myocardial infarction and coronary thrombus. These differences in the color of thrombus associated with unstable angina or myocardial infarction were statistically significant. Although the study of Mizuno et al. (36) did not provide pathologic confirmation of the composition of thrombus, the gross angiographic description is similar to previously reported pathologic descriptions of platelet thrombus (grayish-white) and predominant fibrin thrombus (red or mixed white and red) (37,38). Because most patients with unstable angina had nonocclusive thrombus whereas occlusive thrombus was usually seen in those with myocardial infarction, it is unclear whether these data are simply a reflection of the presence of total occlusion.

IV. Biochemical

If intracoronary thrombus is present in the acute coronary syndromes, biochemical evidence for platelet activation or fibrin formation or fibrin(ogen)olysis may be present. Furthermore, if the thrombus theoretically is larger in acute myocardial infarction than in unstable angina one might expect a greater release of these substances in the circulation after acute myocardial infarction. It is my opinion that the biochemical data neither confirm nor refute the hypothesis that more thrombus is present in myocardial infarction than in unstable angina. However, because so much has been written on this subject, a review of these data seems warranted.

Fibrinopeptide A. When fibrinogen is cleaved by thrombin, fibrinopeptide A is released. This 16-amino acid frag-

ment of the alpha chain of fibrinogen has been assayed by several investigators (39-41). Elevated levels of fibrinopeptide A have often been found in both unstable angina and acute myocardial infarction. In some studies the elevation has been similar in the two syndromes, but at least one study (40) found higher levels in patients with Q wave than in those with non-Q wave infarction or with ischemic chest pain in whom myocardial infarction was excluded. Because fibrinopeptide A levels in patients with a very large intravascular thrombus (larger than in the acute coronary syndromes), as in pulmonary embolism and deep vein thrombosis, are often in the same range as fibrinopeptide A levels reported in the acute coronary syndromes (42), it is likely that fibrinopeptide A determinations cannot distinguish the amount of intravascular thrombus formation. Furthermore, the presence or concentration of fibrin degradation products does not correlate with the level of fibrinopeptide A (43). As the half-life of fibrinopeptide A is only 5 min, the lack of correlation between presumed thrombus size and fibrinopeptide A levels suggests little or no on-going thrombin generation in some cases. Elevated levels of circulating thrombin-antithrombin III complexes, another plasma marker for enhanced thrombin activity, were demonstrated in a preliminary investigation (44) in unstable angina and acute myocardial infarction. Although levels were higher in myocardial infarction the differences were not significant. Again, it is unlikely that thrombus size should correlate with thrombin-antithrombin III levels in the different acute coronary syndromes.

D-dimer. This is a major breakdown product of plasmin on fibrin and has also been reported in acute coronary syndromes. In acute myocardial infarction, D-dimer levels may be normal before thrombolysis, whereas significant increases occur after thrombolytic therapy (45). In unstable angina the data are controversial (10,46). One study (10) reported an increase similar to that found in acute myocardial infarction; in another study (46) D-dimer levels in patients with unstable angina were no higher than levels in a control group of patients with stable angina.

Type I plasminogen activator inhibitor (PAI-1). This is the primary regulator of endogenous plasminogen activation (47) and has also been studied in these syndromes. Several studies have (48-50) reported higher levels of PAI-1 in patients after myocardial infarction. Elevations have also been found during acute myocardial infarction, although its significance in this setting has been questioned (51). High levels of PAI-1 have been associated with coronary reocclusion after thrombolytic therapy (52). Again, the data on PAI-1 in unstable angina are controversial (46,53). Elevations of PAI-1 were found in one study (53), whereas we (46) were unable to find any differences between unstable and stable angina even when sampling was done from the coronary sinus.

Platelet activation. Evidence of platelet activation has also been studied in both acute coronary syndromes. Because arterial thrombi are platelet rich, platelets have been

implicated in the growth of thrombus, embolization of thrombus to the distal vessel, reocclusion after successful thrombolysis and in ischemia secondary to the release of vasoactive substances. Assays utilized to assess platelet hyperactivity may give spurious results because of *in vitro* platelet activation during blood sampling. Measurement of urinary metabolites avoids this problem and urinary levels of the stable metabolites of thromboxane and prostacyclin have been reported in unstable angina. Fitzgerald et al. (23) found elevations of thromboxane and prostacyclin after episodes of spontaneous angina in patients with unstable angina but not during effort-induced angina. Similar studies with these metabolites are not, to my knowledge, available for acute myocardial infarction. Additionally, the simultaneous measurement of these platelet metabolites and fibrin markers has not been reported in any of the acute coronary syndromes.

Determinants of Intracoronary Thrombus Formation

More than 100 years ago Virchow proposed a triad of factors predisposing to thrombosis: vessel wall injury, coagulation and stasis of blood flow. This triad provides a basis for explaining and differentiating intracoronary thrombus formation in the acute syndromes.

1. Vessel wall injury. Plaque disruption represents a form of deep arterial injury to the vessel wall. Plaques that disrupt clinically are usually found on pathologic examination to have a core of extracellular lipid contained underneath their fibrous cap. Thinning of the fibrous cap can often be demonstrated at the site of disruption where infiltration by foam cells or macrophages, or both, is commonly found (54). Experimentally, the depth of injury appears to be an important determinant of the amount of thrombus formation (55,56). Superficial intimal injury to the vessel wall which might be present in some plaque fissures is associated with less platelet deposition than that seen after deep injury with exposure of the media. The degree of platelet deposition in this experimental situation is also dependent on the shear rate, indicating the importance of the interplay between the vessel wall and blood flow in determining the degree of thrombus formation. It has also been suggested that other local wall factors modulate the degree of thrombosis including surface area and configuration of the deep injury, the type of collagen contained within the plaque, the presence of a lipid pool of fatty gruel, tissue thromboplastin levels within the atherosclerotic plaque, prostacyclin production and thrombin content of the lesion (57).

2. Coagulation. A hypercoagulable state due to increased thrombotic activity or a relative decrease in fibrinolytic activity may be responsible for formation of a large thrombus after plaque disruption. Clinically, there are ample data demonstrating hypercoagulability in some patients with acute myocardial infarction. Although these data do not indicate cause and effect, they provide circumstantial evi-

dence for such an association. Hypercoagulability correlates with the more frequent occurrence of acute myocardial infarction in the early morning hours than at other times of day, presumably related at least in part to greater platelet aggregability after assumption of the upright position (58). The recent report (59) of a significant decrease in the incidence of myocardial infarction in the early morning hours with long-term aspirin therapy further supports the importance of increased platelet aggregation as a risk factor for the occurrence of myocardial infarction. Hypercoagulability is also suggested by studies (60,61) showing that elevated fibrinogen levels or Factor VII coagulant activity directly correlates with the future risk of acute myocardial infarction. Cigarette smoking is a risk factor for acute myocardial infarction (62). Chronic cigarette smokers have increased fibrinogen levels as well as increased platelet aggregation. PAI-1 levels have been directly correlated with the incidence of reinfarction in young patients who sustained a myocardial infarction (63). Other data suggesting hypercoagulability might be elevated levels of either beta-thromboglobulin or lipoprotein (a) in survivors of acute myocardial infarction (64,65). Other thrombotic syndromes, such as stroke and sudden death, have an early morning peak similar to that for acute myocardial infarction, suggesting that hypercoagulability is a potential risk factor for other disorders of intravascular thrombosis (66).

3. Blood flow. Stasis predisposes to thrombus, presumably by increasing clot propagation secondary to fibrin deposition. Therefore, whatever decreases flow in the coronary artery—factors related to the plaque or thrombus, heightened vasoconstriction or other hemodynamic factors—will predispose to total occlusion or diminished flow leading to fibrin formation. In a computer model of plaque disruption involving only a moderate (60%) stenosis, Santamore et al. (67) showed that with a dynamic stenosis only a small amount of thrombus may be required initially for the occurrence of myocardial infarction. Intense vasoconstriction with passive lumen collapse may lead to total coronary occlusion, which could then lead to further thrombus formation.

Even in the absence of total occlusion, high shear rates at the site of a significant stenosis will predispose to increased platelet deposition by forcing more platelets to the periphery where they may be deposited at sites of vascular injury (68). Clinically, changing patterns of blood flow modulate the degree of ischemia and infarction. Within the first few hours of infarction alterations in antegrade flow have been commonly detected as spontaneous and nitroglycerin-induced opening and closing of the culprit artery on angiography (69). In unstable angina, increased vasomotion related to either enhanced secretion of vasoconstrictor substances or a relative decrease in vasodilator substances, or both, may cause ischemia by modulating distal perfusion. Conceivably, embolization of thrombotic material to the distal vascular bed may also predispose to alterations in blood flow. The pathogenesis of non-Q wave infarction is presum-

ably associated in many cases with early spontaneous reperfusion of a totally occluded artery (70).

Conclusions

The amount of thrombus developing after coronary plaque disruption may be an important determinant of the acute clinical syndrome. In general, acute myocardial infarction is associated with a larger thrombus than is unstable angina. In acute myocardial infarction the thrombus is occlusive and contains more fibrin. In unstable angina, the thrombus is mural and nonocclusive and may be relatively more rich in platelets. These differences explain both the variable angiographic incidence of total occlusion and response to thrombolytic agents in the two syndromes.

Thrombus formation is a continuous rather than a dichotomous variable. The amount of thrombus varies according to the interplay among vessel injury, coagulation and blood flow. The degree of vessel wall injury or hypercoagulability or stasis of flow, or combinations of these, may turn a benign plaque disruption or fissure into a clinical catastrophe associated with thrombotic occlusion. Vasoconstriction in an artery with a lesion initially responsible for unstable ischemia may secondarily lead to stasis and fibrin formation, thus converting unstable angina to myocardial infarction. Excessive vasoconstriction at or distal to the site of plaque disruption may also be responsible for myocardial infarction even without preceding clinical instability.

It is important to emphasize that the clinical syndrome that develops is the net result of all factors that influence the balance between coronary blood supply and myocardial oxygen demand. For example, if a plaque that is severely stenotic develops a fissure and thrombosis occurs, the clinical syndrome may vary from no change in angina pectoris to unstable angina or even to acute infarction depending on such factors as how acute the obstruction develops, what is the duration of occlusion and whether collateral vessels can be immediately recruited to offset the decrease in antero-grade blood supply. The contribution of each of these factors to the clinical syndrome in an individual patient is difficult to determine. Furthermore, transient vasoconstriction and increased myocardial oxygen demand must also be considered as important determinants of ischemic episodes (71) as well as potentially modifying the degree of infarction. As another example, if a plaque that is only mildly stenotic disrupts with a resultant total occlusion, the likelihood will be a large acute infarction. However, if the thrombus is only nonocclusive or the occlusion develops slowly or is rapidly followed by spontaneous reperfusion, then myocardial infarction may be avoided or limited. Whether more aggressive antithrombotic or antiplatelet therapy (e.g., antithrombin agents), or both, will clinically modify the course of thrombosis in these syndromes remains to be determined.

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